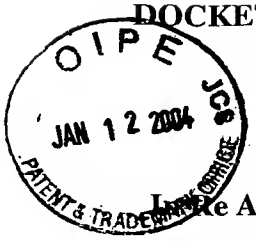
01-14-04

DAC #9 SEQ

DOCKET NO.: PH 7201 (BMS-2201) PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Alan P. Carpenter, Jr.

Serial No.: 09/995,388 Group Art Unit: 1791

Filing Date: November 27, 2001 Examiner: Dameron Levest Jones

For: SIMULTANEOUS IMAGING OF CARDIAC PERFUSION AND A VITRONECTIN RECEPTOR TARGETED IMAGING AGENT

EXPRESS MAIL LABEL NO: EV316304590US
DATE OF DEPOSIT: January 12, 2004

Attention: Office of Petitions
Box DAC
Assistant Commissioner for Patents
Washington, DC 20231

PETITION TO ACCEPT UNINTENTIONALLY DELAYED CLAIM FOR PRIORITY PURSUANT TO 37 CFR §1.78(c)(3)

Applicants hereby advise the Office that they failed to file a timely and proper claim of priority under 35 U.S.C. §§ 119(e), 120, 121 or 365(c) within the later of four months from the filing date of the later filed application or sixteen months from the filing date of the prior-filed application. Accordingly, Applicant(s) hereby petition that the office accept the delayed claims for priority.

Accompanying this petition is:

1. An amendment directing entry of the claim for priority into the specification of the above-identified application;

2. The fee of $1330.00 as set forth in 37 CFR §1.17(t).

STATEMENT

The entire delay in filing the required reply from the due date for the reply until the filing of a grantable petition under 37 CFR 1.137(b) was unintentional.

Payment of fee(s):

- ☒ Enclosed please find a check in the amount of $1330.00.
- ☒ Please charge Deposit Account No. 23-3050 for any fee deficiency or credit this account for any overpayment for this petition.
- ☒ This Petition is enclosed in duplicate.

Date: January 12, 2004

Phillip A. Singer

Phillip A. Singer
Registration No. **40,176**

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: PH 7201 (BMS-2201) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Alan P. Carpenter, Jr.

Application No.: **09/995,388**

Filing Date: **November 27, 2001**

Confirmation No.: **1791**

Group Art Unit: **1616**

Examiner: **Dameron Levest Jones**

For: **SIMULTANEOUS IMAGING OF CARDIAC PERFUSION AND A VITRONECTIN RECEPTOR TARGETED IMAGING AGENT**

EXPRESS MAIL LABEL NO: EV316304590US
DATE OF DEPOSIT: January 12, 2004

EV316304590US

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REPLY TRANSMITTAL LETTER

☐ A Preliminary Amendment.

☒ An Amendment Responsive to the Office Action dated September 10, 2003.

☒ Petition under 37 CFR § 1.144 and 1.181 is enclosed.

☐ An Amendment Supplemental to the Paper filed .

☐ A Substitute Specification (pages 1 -) in clean form.

☐ A substitute specification (pages 1 -) with markings.

☐ An Abstract is enclosed.

☒ A New Declaration and Power of Attorney is enclosed.

☒ A Petition to Accept Unintentionally Delayed Claim for Priority is attached.

☒ An Associate Power of Attorney is enclosed.

☒ A New Sequence Listing consisting of pages 1-12.

☒ Diskette containing Sequence Listing is enclosed.

☐ The computer readable form in the above-identified application is identical with that filed in Application Number , filed . In accordance with 37 CFR § 1.821(e), please use the sequence listing filed on and received by the PTO on as the computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application.

☒ A paper copy of the Sequence Listing:

☐ was filed in the above-identified parent application on and received by the PTO on .

☒ is included herewith.

☒ A Statement to Support Submission of Sequence Information is enclosed.

☐ Other

☐ **No Additional Fee is Due.**

☐ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27.

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as .

☐ This application is no longer entitled to small entity status. It is requested that this be noted in the files of the U.S. Patent and Trademark Office.

				SMALL ENTITY		NOT SMALL ENTITY	
	REMAINING AFTER AMENDMENT	HIGHEST PAID FOR	EXTRA	RATE	FEE	RATE	FEE
TOTAL CLAIMS	66	66 (20 MINIMUM)	0	$9 EACH	$	$18 EACH	$ 0
INDEP. CLAIMS	1	3 (3 MINIMUM)	0	$43 EACH	$	$86 EACH	$ 0
FIRST PRESENTATION OF MULTIPLE DEPENDENT				$145	$	$290	$
☒ ONE MONTH EXTENSION OF TIME				$55	$	$110	$110
☐ TWO MONTH EXTENSION OF TIME				$210	$	$420	$
☐ THREE MONTH EXTENSION OF TIME				$475	$	$950	$
☐ FOUR MONTH EXTENSION OF TIME				$740	$	$1480	$
☐ FIVE MONTH EXTENSION OF TIME				$1005	$	$2010	$
☐ LESS ANY EXTENSION FEE ALREADY PAID				minus	($)	minus	($)
☐ TERMINAL DISCLAIMER				$55	$	$110	$
☐ OTHER FEE OR SURCHARGE AS FOLLOWS:							
TOTAL FEE DUE					$		**$110.00**

☐ A check in the amount of **$ .00** is attached. Please charge any deficiency or credit any overpayment to Deposit Account 23-3050.

☒ Please charge Deposit Account No. 23-3050 in the amount of **$110.00**. This sheet is attached in duplicate.

☒ Petition is hereby made under 37 CFR § 1.136(a) (fees: 37 CFR § 1.17(a)(1)-(4)) to extend the time for response to the Office Action of September 10, 2003 to and through January 12, 2004 (January 10, 2004 is a Saturday) comprising an extension of the shortened statutory period of one month.

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.

Date: January 12, 2004

Phillip A. Singer
Registration No. 40,176

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One Liberty Place - 46th Floor
Philadelphia PA 19103
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DOCKET NO.: PH 7201 (BMS-2201) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Alan P. Carpenter, Jr.

Serial No.: 09/995,388 Group Art Unit: 1791

Filing Date: November 27, 2001 Examiner: Dameron Levest Jones

For: SIMULTANEOUS IMAGING OF CARDIAC PERFUSION AND A VITRONECTIN RECEPTOR TARGETED IMAGING AGENT

EXPRESS MAIL LABEL NO: EV316304590US
DATE OF DEPOSIT: January 12, 2004

Attention: Office of Petitions
Box DAC
Assistant Commissioner for Patents
Washington, DC 20231

PETITION TO ACCEPT UNINTENTIONALLY DELAYED CLAIM FOR PRIORITY PURSUANT TO 37 CFR §1.78(c)(3)

Applicants hereby advise the Office that they failed to file a timely and proper claim of priority under 35 U.S.C. §§ 119(e), 120, 121 or 365(c) within the later of four months from the filing date of the later filed application or sixteen months from the filing date of the prior-filed application. Accordingly, Applicant(s) hereby petition that the office accept the delayed claims for priority.

Accompanying this petition is:

1. An amendment directing entry of the claim for priority into the specification of the above-identified application;

2. The fee of $1330.00 as set forth in 37 CFR §1.17(t).

STATEMENT

The entire delay in filing the required reply from the due date for the reply until the filing of a grantable petition under 37 CFR 1.137(b) was unintentional.

Payment of fee(s):

☒ Enclosed please find a check in the amount of $1330.00.

☒ Please charge Deposit Account No. 23-3050 for any fee deficiency or credit this account for any overpayment for this petition.

☒ This Petition is enclosed in duplicate.

Date: January 12, 2004

Phillip A. Singer

Phillip A. Singer
Registration No. **40,176**

Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia PA 19103
Telephone: (215) 568-3100
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DOCKET NO.: PH 7201 (BMS-2201) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Alan P. Carpenter

Application No.: 09/995,388 **Confirmation No.: 1791**

Filing Date: November 27, 2001 **Group Art Unit: 1616**

Examiner: Dameron James

For: **SIMULTANEOUS IMAGING OF CARDIAC PERFUSION AND A VITRONECTIN RECEPTOR TARGETED IMAGING AGENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ASSOCIATE POWER OF ATTORNEY

The undersigned, of Bristol-Myers Squibb Pharma Company, P.O. Box 4000, Princeton, New Jersey 08543-4000, Attorney(s) and/or Agents for Applicant(s), hereby appoints all attorneys and/or agents associated with Customer No. 23377 with full power to prosecute the above-identified application and to transact all business in the Patent Office connected therewith.

Please continue to direct all correspondence to Paul D. Golian, Esq. at the correspondence address associated with Customer No.

23914
23914
PATENT TRADEMARK OFFICE

Date: Nov. 6, 2003

Blair Q. Ferguson
Registration No. 34,329

Bristol-Myers Squibb Pharma Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
Telephone: (302) 467-5260
Facsimile: (302) 467-6701

#12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Alan P. Carpenter, Jr.

Confirmation No.: **1791**

Application No.: **09/995,388**

Group Art Unit: **1616**

Filing Date: **November 27, 2001**

Examiner: **Dameron Levest Jones**

For: **Simultaneous Imaging of Cardiac Perfusion and a Vitronectin Receptor Targeted Imaging Agent**

EXPRESS MAIL LABEL NO: EV316304590US
DATE OF DEPOSIT: January 12, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION UNDER 37 CFR § 1.144 AND 1.181

In an Office Action dated September 10, 2003, the Examiner made FINAL the restriction requirement of March 11, 2003. Applicant hereby petitions the Commissioner to review the requirement in view of the following. Applicant requests that the restriction requirement to elect a group of compounds wherein the targeted imaging agent is selected from particular polypeptide sequences be changed to *a species election* of a perfusion imaging agent and *a species election* of a vitronectin receptor targeted imaging agent of a single polypeptide sequence within *a genus* of claim 1.

STATEMENT OF THE FACTS INVOLVED

An Office Action was issued in the above referenced case on March 11, 2003, subjecting claims 1 to 66 to restriction to 18 groups and requiring Applicant to elect a single disclosed species comprising a vitronectin receptor targeted imaging agent and a single disclosed species comprising a perfusion imaging agent. In a Response filed on May 12, 2003, Applicant elected *with traverse* to prosecute the claims of Group XVI. Further, Applicant elected, *with traverse*, a species where the perfusion imaging agent is Tl-201, as described on page 53, ¶ 59, and the vitronectin receptor targeted imaging agent is the ^{99m}Tc-tricine-TPPTS complex of [[5-[carbonyl]-2-pyridinyl]diazenido]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, as described in Example 39, page 200. Applicant further proposed an alternative restriction to four groups of claims. An Office Action dated September 10, 2003 further modified the alternative four groups of claims, and the restriction to modified Group I was made final.

Application as filed

The above referenced case was filed on November 27, 2001 with claims 1-66 drawn to methods of concurrent imaging in a mammal comprising: administering to said mammal a vitronectin receptor targeted imaging agent and a perfusion imaging agent; and concurrently detecting the vitronectin receptor targeted imaging agent bound at the vitronectin receptor and the perfusion imaging agent; and forming an image from the detection of said vitronectin targeted imaging agent and said perfusion imaging agent. The original claims read as follows:

1. (original) A method of concurrent imaging in a mammal comprising:

   a) administering to said mammal a vitronectin receptor targeted imaging agent and a perfusion imaging agent; and

   b) concurrently detecting the vitronectin receptor targeted imaging agent bound at the vitronectin receptor and the perfusion imaging agent; and

   c) forming an image from the detection of said vitronectin targeted imaging agent and said perfusion imaging agent.

2. (original) The method of claim 1, wherein the vitronectin receptor is selected from the group: $\alpha_v\beta_3$, and $\alpha_v\beta_5$.

3. (original) The method according to claim 1, wherein the vitronectin receptor is $\alpha_v\beta_3$.

4. (original) The method of claim 1 wherein the perfusion imaging agent is selected from the group consisting of: an ultrasound perfusion agent, an MRI perfusion imaging agent, and a radiolabelled imaging agent.

5. (original) The method of claim 1 wherein the perfusion imaging agent is hexakis methoxyisobutyl isonitrile Technetium(I) (^{99m}Tc-Sestamibi), ^{210}Tl, ^{99m}Tc-tetrofosmin, ^{99m}Tc-furifosmin, or ^{99m}Tc-NOET.

6. (original) The method according to claim 1,wherein the vitronectin receptor targeted imaging agent is a diagnostic metallopharmaceutical.

7. (original) The method according to claim 6, wherein the vitronectin receptor targeting agent is a vitronectin antagonist.

8. (original) The method according to claim 6, wherein the vitronectin receptor targeting agent is a vitronectin agonist.

9. (original) The method of claim 6, wherein the diagnostic metallopharmaceutical comprises a metal and a compound, wherein the compound comprises:

a)a chelator capable of chelating the metal;

b)a targeting moiety, wherein the targeting moiety is bound to the chelator; and

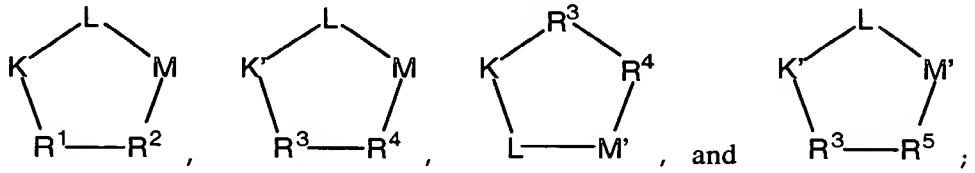
c) 0-1 linking groups between the targeting moiety and the chelator;

wherein the targeting moiety is a peptide or peptidomimetic which binds to a vitronectin receptor.

10. (original) The method according to claim 9, wherein compound is of the formula:

$(Q)_d$-L_n-Ch or $(Q)_d$-L_n-$(Ch)_{d'}$

wherein, Q is a peptide independently selected from the group:



K is an L-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ-N-2-imidazolinylornithine, δ-N-benzylcarbamoylornithine, and β-2-benzimidazolylacetyl-1,2-diaminopropionic acid;

K' is a D-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ-N-2-imidazolinylornithine, δ-N-benzylcarbamoylornithine, and β-2-benzimidazolylacetyl-1,2-diaminopropionic acid;

L is independently selected at each occurrence from the group: glycine, L-alanine, and D-alanine;

M is L-aspartic acid;

M' is D-aspartic acid;

R^1 is an amino acid substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, phenylalanine, thienylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, 1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, and methionine;

R^2 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, methionine, and 2-aminothiazole-4-acetic acid;

R^3 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, and D-methionine;

R^4 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, D-methionine, and 2-aminothiazole-4-acetic acid;

R^5 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-2-aminohexanoic acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-serine, L-ornithine,

L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, L-cysteine, L-penicillamine, L-methionine, and 2-aminothiazole-4-acetic acid;

provided that one of R^1, R^2, R^3, R^4, and R^5 in each Q is substituted with a bond to L_n,

further provided that when R^2 is 2-aminothiazole-4-acetic acid, K is N-methylarginine, further provided that when R^4 is 2-aminothiazole-4-acetic acid, K and K' are N-methylarginine, and still further provided that when R^5 is 2-aminothiazole-4-acetic acid, K' is N-methylarginine;

d is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

L_n is a linking group having the formula:

$$(CR^6R^7)_g\text{-}(W)_h\text{-}(CR^{6a}R^{7a})_{g'}\text{-}(Z)_k\text{-}(W)_{h'}\text{-}(CR^8R^9)_{g''}\text{-}(W)_{h''}\text{-}(CR^{8a}R^{9a})_{g'''}$$

provided that g+h+g'+k+h'+g"+h"+g'" is other than 0;

W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO_2, $(OCH_2CH_2)_s$, $(CH_2CH_2O)_{s'}$, $(OCH_2CH_2CH_2)_{s''}$, $(CH_2CH_2CH_2O)_t$, and $(aa)_{t'}$;

aa is independently at each occurrence an amino acid;

Z is selected from the group: aryl substituted with 0-3 R^{10}, $C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^{10}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{10};

R^6, R^{6a}, R^7, R^{7a}, R^8, R^{8a}, R^9 and R^{9a} are independently selected at each occurrence from the group: H, =O, COOH, SO_3H, PO_3H, C_1-C_5 alkyl substituted with 0-3 R^{10}, aryl

substituted with 0-3 R^{10}, benzyl substituted with 0-3 R^{10}, and C_1-C_5 alkoxy substituted with 0-3 R^{10}, $NHC(=O)R^{11}$, $C(=O)NHR^{11}$, $NHC(=O)NHR^{11}$, NHR^{11}, R^{11}, and a bond to C_h;

R^{10} is independently selected at each occurrence from the group: a bond to C_h, $COOR^{11}$, OH, NHR^{11}, SO_3H, PO_3H, aryl substituted with 0-3 R^{11}, C_{1-5} alkyl substituted with 0-1 R^{12}, C_{1-5} alkoxy substituted with 0-1 R^{12}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{11};

R^{11} is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R^{12}, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R^{12}, C_{3-10} cycloalkyl substituted with 0-1 R^{12}, polyalkylene glycol substituted with 0-1 R^{12}, carbohydrate substituted with 0-1 R^{12}, cyclodextrin substituted with 0-1 R^{12}, amino acid substituted with 0-1 R^{12}, polycarboxyalkyl substituted with 0-1 R^{12}, polyazaalkyl substituted with 0-1 R^{12}, peptide substituted with 0-1 R^{12}, wherein the peptide is comprised of 2-10 amino acids, and a bond to C_h;

R^{12} is a bond to C_h;

k is selected from 0, 1, and 2;
h is selected from 0, 1, and 2;
h' is selected from 0, 1, 2, 3, 4, and 5;
h" is selected from 0, 1, 2, 3, 4, and 5;
g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
g" is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

g"' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

s is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

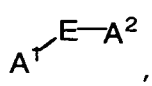
s' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

s" is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

t is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

C_h is a metal bonding unit having a formula selected from the group: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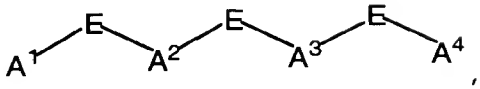
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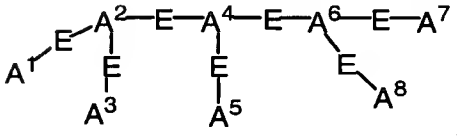
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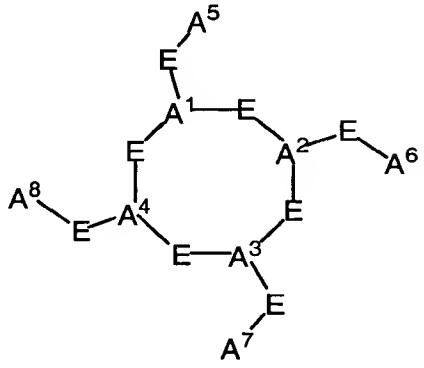

;

A^1, A^2, A^3, A^4, A^5, A^6, A^7, and A^8 are independently selected at each occurrence from the group N, NR^{13}, $NR^{13}R^{14}$, S, SH, O, OH, PR^{13}, $PR^{13}R^{14}$, $P(O)R^{15}R^{16}$, and a bond to L_n;

E is a bond, CH, or a spacer group independently selected at each occurrence from the group: C_1-C_{10} alkyl substituted with 0-3 R^{17}, aryl substituted with 0-3 R^{17}, C_{3-10} cycloalkyl substituted with 0-3 R^{17}, heterocyclo-C_{1-10} alkyl substituted with 0-3 R^{17}, wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, C_{6-10}

aryl-C_{1-10} alkyl substituted with 0-3 R^{17}, C_{1-10} alkyl-C_{6-10} aryl- substituted with 0-3 R^{17}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17};

R^{13}, and R^{14} are each independently selected from the group: a bond to L_n, hydrogen, C_1-C_{10} alkyl substituted with 0-3 R^{17}, aryl substituted with 0-3 R^{17}, C_{1-10} cycloalkyl substituted with 0-3 R^{17}, heterocyclo-C_{1-10} alkyl substituted with 0-3 R^{17}, wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, C_{6-10} aryl-C_{1-10} alkyl substituted with 0-3 R^{17}, C_{1-10} alkyl-C_{6-10} aryl- substituted with 0-3 R^{17}, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17}, and an electron, provided that when one of R^{13} or R^{14} is an electron, then the other is also an electron;

alternatively, R^{13} and R^{14} combine to form $=C(R^{20})(R^{21})$;

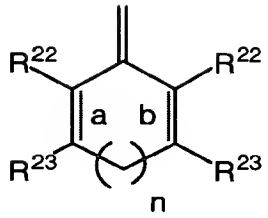
R^{15} and R^{16} are each independently selected from the group: a bond to L_n, -OH, C_1-C_{10} alkyl substituted with 0-3 R^{17}, C_1-C_{10} alkyl substituted with 0-3 R^{17}, aryl substituted with 0-3 R^{17}, C_{3-10} cycloalkyl substituted with 0-3 R^{17}, heterocyclo-C_{1-10} alkyl substituted with 0-3 R^{17}, wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, C_{6-10} aryl-C_{1-10} alkyl substituted with 0-3 R^{17}, C_{1-10} alkyl-C_{6-10} aryl- substituted with 0-3 R^{17}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17};

R^{17} is independently selected at each occurrence from the group: a bond to L_n, =O, F, Cl, Br, I, $-CF_3$, -CN, $-CO_2R^{18}$, $-C(=O)R^{18}$, $-C(=O)N(R^{18})_2$, -CHO, $-CH_2OR^{18}$, $-OC(=O)R^{18}$, $-OC(=O)OR^{18a}$, $-OR^{18}$, $-OC(=O)N(R^{18})_2$, $-NR^{19}C(=O)R^{18}$, $-NR^{19}C(=O)OR^{18a}$, $-NR^{19}C(=O)N(R^{18})_2$, $-NR^{19}SO_2N(R^{18})_2$, $-NR^{19}SO_2R^{18a}$, $-SO_3H$, $-SO_2R^{18a}$, $-SR^{18}$, $-S(=O)R^{18a}$, $-SO_2N(R^{18})_2$, $-N(R^{18})_2$, $-NHC(=S)NHR^{18}$, $=NOR^{18}$, NO_2, $-C(=O)NHOR^{18}$, $-C(=O)NHNR^{18}R^{18a}$, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_5 alkyl, C_2-C_4 alkenyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_2-C_6 alkoxyalkyl, aryl substituted with 0-2 R^{18}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

R^{18}, R^{18a}, and R^{19} are independently selected at each occurrence from the group: a bond to L_n, H, C_1-C_6 alkyl, phenyl, benzyl, C_1-C_6 alkoxy, halide, nitro, cyano, and trifluoromethyl;

R^{20} and R^{21} are independently selected from the group: H, C_1-C_{10} alkyl, -CN, $-CO_2R^{25}$, $-C(=O)R^{25}$, $-C(=O)N(R^{25})_2$, C_2-C_{10} 1-alkene substituted with 0-3 R^{23}, C_2-C_{10} 1-alkyne substituted with 0-3 R^{23}, aryl substituted with 0-3 R^{23}, unsaturated 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{23}, and unsaturated C_3-$_{10}$ carbocycle substituted with 0-3 R^{23};

alternatively, R^{20} and R^{21}, taken together with the divalent carbon radical to which they are attached form:



R^{22} and R^{23} are independently selected from the group: H, R^{24}, C_1-C_{10} alkyl substituted with 0-3 R^{24}, C_2-C_{10} alkenyl substituted with 0-3 R^{24}, C_2-C_{10} alkynyl substituted with 0-3 R^{24}, aryl substituted with 0-3 R^{24}, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{24}, and C_{3-10} carbocycle substituted with 0-3 R^{24};

alternatively, R^{22}, R^{23} taken together form a fused aromatic or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

a and b indicate the positions of optional double bonds and n is 0 or 1;

R^{24} is independently selected at each occurrence from the group: =O, F, Cl, Br, I, $-CF_3$, -CN, $-CO_2R^{25}$, $-C(=O)R^{25}$, $-C(=O)N(R^{25})_2$, $-N(R^{25})_3^+$, $-CH_2OR^{25}$, $-OC(=O)R^{25}$, $-OC(=O)OR^{25a}$, $-OR^{25}$, $-OC(=O)N(R^{25})_2$, $-NR^{26}C(=O)R^{25}$, $-NR^{26}C(=O)OR^{25a}$, $-NR^{26}C(=O)N(R^{25})_2$, $-NR^{26}SO_2N(R^{25})_2$, $-NR^{26}SO_2R^{25a}$, $-SO_3H$, $-SO_2R^{25a}$, $-SR^{25}$, $-S(=O)R^{25a}$, $-SO_2N(R^{25})_2$, $-N(R^{25})_2$, $=NOR^{25}$, $-C(=O)NHOR^{25}$, $-OCH_2CO_2H$, and 2-(1-morpholino)ethoxy; and,

R^{25}, R^{25a}, and R^{26} are each independently selected at each occurrence from the group: hydrogen and C_1-C_6 alkyl;

and a pharmaceutically acceptable salt thereof.

11. (original) The method according to claim 10 wherein

L is glycine;

R^1 is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, tyrosine, phenylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, lysine, ornithine, 1,2-diaminobutyric acid, and 1,2-diaminopropionic acid;

R^2 is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, and 2-aminothiazole-4-acetic acid;

R^3 is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-tyrosine, D-phenylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, and D-1,2-diaminopropionic acid;

R^4 is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, and 2-aminothiazole-4-acetic acid;

R^5 is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine,

L-lysine, L-ornithine, L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, and 2-aminothiazole-4-acetic acid;

d is selected from 1, 2, and 3;

W is independently selected at each occurrence from the group: O, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO_2, $(OCH_2CH_2)_s$, $(CH_2CH_2O)_{s'}$, $(OCH_2CH_2CH_2)_{s''}$, and $(CH_2CH_2CH_2O)_t$,

Z is selected from the group: aryl substituted with 0-1 R^{10}, C_{3-10} cycloalkyl substituted with 0-1 R^{10}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R^{10};

R^6, R^{6a}, R^7, R^{7a}, R^8, R^{8a}, R^9, and R^{9a} are independently selected at each occurrence from the group: H, =O, COOH, SO_3H, C_1-C_5 alkyl substituted with 0-1 R^{10}, aryl substituted with 0-1 R^{10}, benzyl substituted with 0-1 R^{10}, and C_1-C_5 alkoxy substituted with 0-1 R^{10}, $NHC(=O)R^{11}$, $C(=O)NHR^{11}$, $NHC(=O)NHR^{11}$, NHR^{11}, R^{11}, and a bond to C_h;

R^{10} is independently selected at each occurrence from the group: $COOR^{11}$, OH, NHR^{11}, SO_3H, aryl substituted with 0-1 R^{11}, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R^{11}, C_1-C_5 alkyl substituted with 0-1 R^{12}, C_1-C_5 alkoxy substituted with 0-1 R^{12}, and a bond to C_h;

R^{11} is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R^{12}, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R^{12}, polyalkylene glycol substituted with 0-1 R^{12}, carbohydrate substituted with 0-1 R^{12}, cyclodextrin substituted with 0-1 R^{12}, amino acid substituted with 0-1 R^{12}, and a bond to C_h;

k is 0 or 1;

h is 0 or 1;

h' is 0 or 1;

s is selected from 0, 1, 2, 3, 4, and 5;

s' is selected from 0, 1, 2, 3, 4, and 5;

s" is selected from 0, 1, 2, 3, 4, and 5;

t is selected from 0, 1, 2, 3, 4, and 5;

A^1, A^2, A^3, A^4, A^5, A^6, A^7, and A^8 are independently selected at each occurrence from the group: NR^{13}, $NR^{13}R^{14}$, S, SH, OH, and a bond to L_n;

E is a bond, CH, or a spacer group independently selected at each occurrence from the group: C_1-C_{10} alkyl substituted with 0-3 R^{17}, aryl substituted with 0-3 R^{17}, C_{3-10} cycloalkyl substituted with 0-3 R^{17}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17};

R^{13}, and R^{14} are each independently selected from the group: a bond to L_n, hydrogen, C_1-C_{10} alkyl substituted with 0-3 R^{17}, aryl substituted with 0-3 R^{17}, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17}, and an electron, provided that when one of R^{13} or R^{14} is an electron, then the other is also an electron;

alternatively, R^{13} and R^{14} combine to form $=C(R^{20})(R^{21})$;

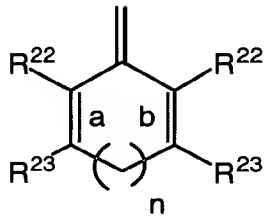
R^{17} is independently selected at each occurrence from the group: a bond to L_n, =O, F, Cl, Br, I, $-CF_3$, -CN, $-CO_2R^{18}$, $-C(=O)R^{18}$, $-C(=O)N(R^{18})_2$, $-CH_2OR^{18}$, $-OC(=O)R^{18}$, $-OC(=O)OR^{18a}$, $-OR^{18}$, $-OC(=O)N(R^{18})_2$, $-NR^{19}C(=O)R^{18}$, $-NR^{19}C(=O)OR^{18a}$, $-NR^{19}C(=O)N(R^{18})_2$, $-NR^{19}SO_2N(R^{18})_2$, $-NR^{19}SO_2R^{18a}$, $-SO_3H$, $-SO_2R^{18a}$,

$-S(=O)R^{18a}$, $-SO_2N(R^{18})_2$, $-N(R^{18})_2$, $-NHC(=S)NHR^{18}$, $=NOR^{18}$, $-C(=O)NHNR^{18}R^{18a}$, $-OCH_2CO_2H$, and 2-(1-morpholino)ethoxy;

R^{18}, R^{18a}, and R^{19} are independently selected at each occurrence from the group: a bond to L_n, H, and C_1-C_6 alkyl;

R^{20} and R^{21} are independently selected from the group: H, C_1-C_5 alkyl, $-CO_2R^{25}$, C_2-C_5 1-alkene substituted with 0-3 R^{23}, C_2-C_5 1-alkyne substituted with 0-3 R^{23}, aryl substituted with 0-3 R^{23}, and unsaturated 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{23};

alternatively, R^{20} and R^{21}, taken together with the divalent carbon radical to which they are attached form:



R^{22} and R^{23} are independently selected from the group: H, and R^{24};

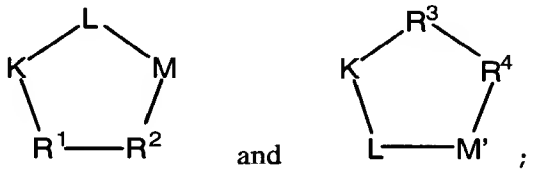
alternatively, R^{22}, R^{23} taken together form a fused aromatic or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

R^{24} is independently selected at each occurrence from the group: $-CO_2R^{25}$, $-C(=O)N(R^{25})_2$, $-CH_2OR^{25}$, $-OC(=O)R^{25}$, $-OR^{25}$, $-SO_3H$, $-N(R^{25})_2$, and $-OCH_2CO_2H$; and,

R^{25} is independently selected at each occurrence from the group: H and C_1-C_3 alkyl.

12. The method according to claim 10 wherein

Q is a peptide selected from the group:



;

R^1 is L-valine, D-valine, D-lysine optionally substituted on the ε amino group with a bond to L_n or L-lysine optionally substituted on the ε amino group with a bond to L_n;

R^2 is L-phenylalanine, D-phenylalanine, D-1-naphthylalanine, 2-aminothiazole-4-acetic acid, L-lysine optionally substituted on the ε amino group with a bond to L_n or tyrosine, the tyrosine optionally substituted on the hydroxy group with a bond to L_n;

R^3 is D-valine, D-phenylalanine, or L-lysine optionally substituted on the ε amino group with a bond to L_n;

R^4 is D-phenylalanine, D-tyrosine substituted on the hydroxy group with a bond to L_n, or L-lysine optionally substituted on the ε amino group with a bond to L_n;

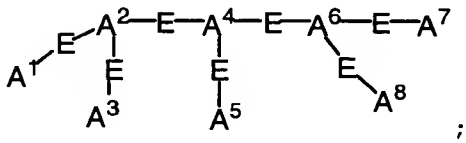
provided that one of R^1 and R^2 in each Q is substituted with a bond to L_n, and further provided that when R^2 is 2-aminothiazole-4-acetic acid, K is N-methylarginine;

d is 1 or 2;

W is independently selected at each occurrence from the group: NHC(=O), C(=O)NH, C(=O), $(CH_2CH_2O)_{s'}$, and $(CH_2CH_2CH_2O)_t$;

R^6, R^{6a}, R^7, R^{7a}, R^8, R^{8a}, R^9, and R^{9a} are independently selected at each occurrence from the group: H, $NHC(=O)R^{11}$, and a bond to C_h;

k is 0;
h" is selected from 0, 1, 2, and 3;
g is selected from 0, 1, 2, 3, 4, and 5;
g' is selected from 0, 1, 2, 3, 4, and 5;
g" is selected from 0, 1, 2, 3, 4, and 5;
g"' is selected from 0, 1, 2, 3, 4, and 5;
s' is 1 or 2;
t is 1 or 2;

C_h is 

;

A^1 is selected from the group: OH, and a bond to L_n;

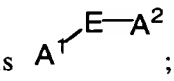
A^2, A^4, and A^6 are each N;

A^3, A^5, and A^8 are each OH;

A^7 is a bond to L_n or NH-bond to L_n;

E is a C_2 alkyl substituted with 0-1 R^{17};

R^{17} is =O;

alternatively, C_h is  ;

A^1 is NH_2 or $N=C(R^{20})(R^{21})$;

E is a bond;

A^2 is NHR^{13};

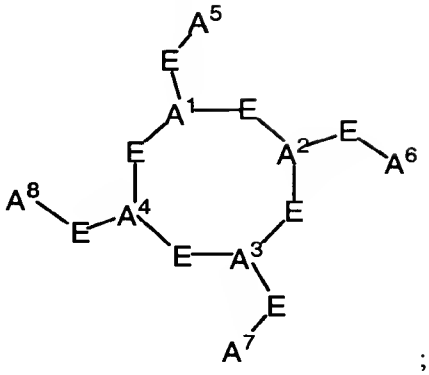
R^{13} is a heterocycle substituted with R^{17}, the heterocycle being selected from pyridine and pyrimidine;

R^{17} is selected from a bond to L_n, $C(=O)NHR^{18}$, and $C(=O)R^{18}$;

R^{18} is a bond to L_n;

R^{24} is selected from the group: $-CO_2R^{25}$, $-OR^{25}$, $-SO_3H$, and $-N(R^{25})_2$;

R^{25} is independently selected at each occurrence from the group: hydrogen and methyl;

alternatively, C_h is  ;

A^1, A^2, A^3, and A^4 are each N;

A^5, A^6, and A^8 are each OH;

A^7 is a bond to L_n;

E is a C_2 alkyl substituted with 0-1 R^{17}; and,

R^{17} is =O.

13. (original) The method of claim 6 wherein the diagnostic metallopharmaceutical comprises a radioisotope.

14. (original) The method of claim 13 wherein the radioisotope is selected from the group consisting of ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, and ^{68}Ga.

15. (original) The method of claim 14 wherein the radioisotope is selected from the group consisting of In-111, and Tc-99m.

16. (original) The method of claim 9, wherein the metallopharmaceutical is a diagnostic radiopharmaceutical and the metal is a radioisotope selected from the group: ^{99m}Tc, ^{95}Tc, ^{111}In, ^{62}Cu, ^{64}Cu, ^{67}Ga, and ^{68}Ga.

17. (original) The method of claim 16 wherein the radioisotope is selected from the group consisting of ^{111}In, and ^{99m}Tc.

18. (original) The method according to claim 16, wherein the radioisotope is ^{99m}Tc or ^{95}Tc, the radiopharmaceutical further comprises a first ancillary ligand and a second ancillary ligand capable of stabilizing the radiopharmaceutical.

19. (original) The method according to claim 16, wherein the radioisotope is ^{99m}Tc.

20. (original) The method according to claim 19, wherein the radiopharmaceutical is selected from the group:

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val));

^{99m}Tc(tricine)(TPPMS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly));

^{99m}Tc(tricine)(TPPDS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly));

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly));

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Phe-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])));

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])));

^{99m}Tc(tricine)(TPPTS)([[5-[carbonyl]-2-pyridinyl]diazenido]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe});

^{99m}Tc(tricine)(TPPTS)(cyclo{Arg-Gly-Asp-D-Nal-Lys([[5-[carbonyl]-2-pyridinyl]diazenido])});

^{99m}Tc(tricine)(TPPTS)([[5-[carbonyl]-2-pyridinyl]-diazenido]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal});

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr((N-[[5-[carbonyl]-2-pyridinyl]diazenido]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val));

^{99m}Tc(tricine)(TPPTS)(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(Lys-Arg-Gly-Asp-D-Phe))-O-cyclo(Lys-Arg-Gly-Asp-D-Phe));

^{99m}Tc(tricine)(TPPTS)(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp))-O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp));

^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])-D-Val));

^{99m}Tc(tricine)(TPPTS)(cyclo{D-Lys([[5-[carbonyl]-2-pyridinyl]diazenido])-D-Phe-D-Asp-Gly-Arg});

^{99m}Tc(tricine)(TPPTS)([[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg});

^{99m}Tc(tricine)(TPPTS)(cyclo{D-Phe-D-Lys([[5-[carbonyl]-2-pyridinyl]diazenido])-D-Asp-Gly-Arg});

^{99m}Tc(tricine)(TPPTS)(cyclo(N-Me-Arg-Gly-Asp-ATA-D-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])));

^{99m}Tc(tricine)(TPPTS)(cyclo{Cit-Gly-Asp-D-Phe-Lys([[5-[carbonyl]-2-pyridinyl]diazenido])}); and

^{99m}Tc(tricine)(1,2,4-triazole)(cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val)).

21. (original) The method according to claim 16, wherein the radioisotope is ^{111}In.

22. (original) The method according to claim 21, wherein the radiopharmaceutical is selected from the group:
(DOTA-^{111}In)-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe};
cyclo(Arg-Gly-Asp-D-Phe-Lys(DTPA-^{111}In)); and,
cyclo(Arg-Gly-Asp-D-Phe-Lys)$_2$(DTPA-^{111}In).

23. (original) The method according to claim 6 wherein the diagnostic metallopharmaceutical is comprised of a paramagnetic metal.

24. (original) The method according to claim 23 wherein the paramagnetic metal is selected from the group consisting of Gd(III), Dy(III), Fe(III) and Mn(II).

25. (original) The method according to claim 23 wherein the paramagnetic metal is Gd(III).

26. (original) The method according to claim 9, wherein the metal is a paramagnetic metal ion selected from the group Gd(III), Dy(III), Fe(III) and Mn(II).

27. (original) The method according to claim 26, wherein the metal ion is Gd(III).

28. (original) The method according to claim 27, wherein the contrast agent is: cyclo(Arg-Gly-Asp-D-Tyr(N-DTPA(Gd(III))-3-aminopropyl)-Val).

29. (original) The method according to claim 6 wherein the diagnostic metallopharmaceutical is a X-ray contrast agent.

30. (original) The method according to claim 29 wherein the X-ray contrast agent comprises a vitronectin targeting agent; and the metal is selected from the group: Re, Sm, Ho, Lu, Pm, Y, Bi, Pd, Gd, La, Au, Au, Yb, Dy, Cu, Rh, Ag, and Ir.

31. (original) The method according to claim 9, wherein diagnostic metallopharmaceutical is a X-ray contrast agent; the metal is selected from the group: Re, Sm, Ho, Lu, Pm, Y, Bi, Pd, Gd, La, Au, Au, Yb, Dy, Cu, Rh, Ag, and Ir.

32. (original) A kit comprising a compound of claim 9 and a perfusion imaging agent.

33. (original) The kit of Claim 32 further comprising a reducing agent.

34. (original) The kit of Claim 33 wherein the reducing agent is tin(II).

35. (original) The kit of Claim 33 further comprising one or more ancillary ligands.

36. (original) The kit of Claim 35 wherein the ancillary ligands are tricine and TPPTS.

37. (original) A kit comprising a compound of claim 10 and a perfusion imaging agent.

38. (original) A method according to claim 1, wherein the vitronectin targeted imaging agent is a vitronectin targeted ultrasound imaging agent.

39. (original) A method according to Claim 38,wherein the ultrasound imaging agent comprises an echogenic gas or temperature activated gaseous precursor, and a compound, wherein the compound comprises:

a) a surfactant;

b) a targeting moiety, wherein the targeting moiety is bound to the surfactant; and

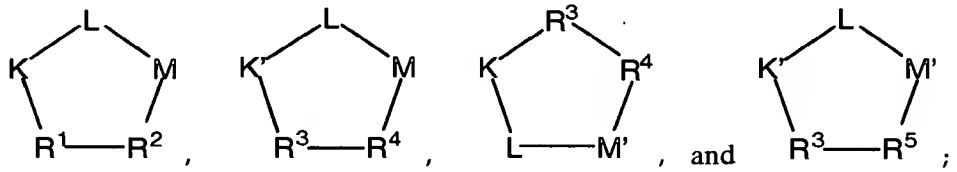
c) 0-1 linking groups between the targeting moiety and surfactant;

wherein the targeting moiety is a peptide or peptidomimetic, which binds to a vitronectin receptor.

40. (original) A method according to Claim 39, wherein the compound is of the formula:

$$(Q)_d\text{-}L_n\text{-}S_f$$

wherein, Q is a cyclic pentapeptide independently selected from the group:



and ;

K is an L-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine,

δ-N-2-imidazolinylornithine, δ-N-benzylcarbamoylornithine, and β-2-benzimidazolylacetyl-1,2-diaminopropionic acid;

K' is a D-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ-N-2-imidazolinylornithine, δ-N-benzylcarbamoylornithine, and β-2-benzimidazolylacetyl-1,2-diaminopropionic acid;

L is independently selected at each occurrence from the group: glycine, L-alanine, and D-alanine;

M is L-aspartic acid;

M' is D-aspartic acid;

R^1 is an amino acid substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, phenylalanine, thienylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, 1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, and methionine;

R^2 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, methionine, and 2-aminothiazole-4-acetic acid;

R^3 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, and D-methionine;

R^4 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, D-methionine, and 2-aminothiazole-4-acetic acid;

R^5 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-2-aminohexanoic acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-serine, L-ornithine, L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, L-cysteine, L-penicillamine, L-methionine, and 2-aminothiazole-4-acetic acid;

provided that one of R^1, R^2, R^3, R^4, and R^5 in each Q is substituted with a bond to L_n,

further provided that when R^2 is 2-aminothiazole-4-acetic acid, K is N-methylarginine, further provided that when R^4 is 2-aminothiazole-4-acetic acid, K

and K' are N-methylarginine, and still further provided that when R^5 is 2-aminothiazole-4-acetic acid, K' is N-methylarginine;

d is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

S_f is a surfactant which is a lipid or a compound of the formula: $A^9-E^1-A^{10}$;

A^9 is selected from the group: OH and OR^{27};

A^{10} is OR^{27};

R^{27} is $C(=O)C_{1\text{-}20}$ alkyl;

E^1 is $C_{1\text{-}10}$ alkylene substituted with 1-3 R^{28};

R^{28} is independently selected at each occurrence from the group: R^{30}, $-PO_3H-R^{30}$, =O, $-CO_2R^{29}$, $-C(=O)R^{29}$, $-C(=O)N(R^{29})_2$, $-CH_2OR^{29}$, $-OR^{29}$, $-N(R^{29})_2$, C_1-C_5 alkyl, and C_2-C_4 alkenyl;

R^{29} is independently selected at each occurrence from the group: R^{30}, H, C_1-C_6 alkyl, phenyl, benzyl, and trifluoromethyl;

R^{30} is a bond to L_n;

L_n is a linking group having the formula:

$$(CR^6R^7)_g\text{-}(W)_h\text{-}(CR^{6a}R^{7a})_{g'}\text{-}(Z)_k\text{-}(W)_{h'}\text{-}(CR^8R^9)_{g''}\text{-}(W)_{h''}\text{-}(CR^{8a}R^{9a})_{g'''}$$

W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO_2, $(OCH_2CH_2)_{20-200}$, $(CH_2CH_2O)_{20-200}$, $(OCH_2CH_2CH_2)_{20-200}$, $(CH_2CH_2CH_2O)_{20-200}$, and $(aa)_t$;

aa is independently at each occurrence an amino acid;

Z is selected from the group: aryl substituted with 0-3 R^{10}, C_{3-10} cycloalkyl substituted with 0-3 R^{10}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{10};

R^6, R^{6a}, R^7, R^{7a}, R^8, R^{8a}, R^9 and R^{9a} are independently selected at each occurrence from the group: H, =O, COOH, SO_3H, PO_3H, C_1-C_5 alkyl substituted with 0-3 R^{10}, aryl substituted with 0-3 R^{10}, benzyl substituted with 0-3 R^{10}, and C_1-C_5 alkoxy substituted with 0-3 R^{10}, $NHC(=O)R^{11}$, $C(=O)NHR^{11}$, $NHC(=O)NHR^{11}$, NHR^{11}, R^{11}, and a bond to S_f;

R^{10} is independently selected at each occurrence from the group: a bond to S_f, $COOR^{11}$, OH, NHR^{11}, SO_3H, PO_3H, aryl substituted with 0-3 R^{11}, C_{1-5} alkyl substituted with 0-1 R^{12}, C_{1-5} alkoxy substituted with 0-1 R^{12}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{11};

R^{11} is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R^{12}, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R^{12}, C_{3-10}

cycloalkyl substituted with 0-1 R^{12}, amino acid substituted with 0-1 R^{12}, and a bond to S_f;

R^{12} is a bond to S_f;

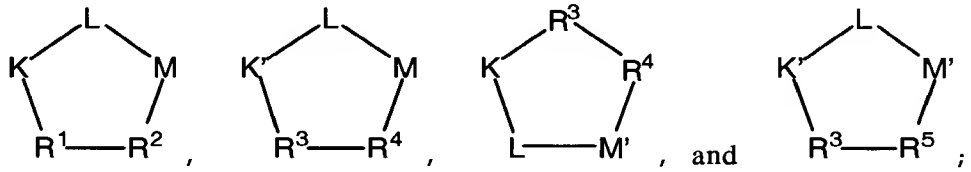
k is selected from 0, 1, and 2;
h is selected from 0, 1, and 2;
h' is selected from 0, 1, 2, 3, 4, and 5;
h" is selected from 0, 1, 2, 3, 4, and 5;
g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
g" is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
g"' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

and a pharmaceutically acceptable salt thereof.

41. (original) A method according to Claim 40, wherein the compound is of the formula:

$$Q\text{-}L_n\text{-}S_f$$

wherein, Q is a cyclic pentapeptide independently selected from the group:



, , , and ;

N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ-N-2-imidazolinylornithine, δ-N-benzylcarbamoylornithine, and β-2-benzimidazolylacetyl-1,2-diaminopropionic acid;

K' is a D-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ-N-2-imidazolinylornithine, δ-N-benzylcarbamoylornithine, and β-2-benzimidazolylacetyl-1,2-diaminopropionic acid;

L is independently selected at each occurrence from the group: glycine, L-alanine, and D-alanine;

M is L-aspartic acid;

M' is D-aspartic acid;

R^1 is an amino acid substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, phenylalanine, thienylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, 1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, and methionine;

R^2 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, methionine, and 2-aminothiazole-4-acetic acid;

R^3 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, and D-methionine;

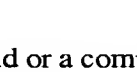
R^4 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, D-methionine, and 2-aminothiazole-4-acetic acid;

R^5 is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-2-aminohexanoic acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-serine, L-ornithine, L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, L-cysteine, L-penicillamine, L-methionine, and 2-aminothiazole-4-acetic acid;

provided that one of R^1, R^2, R^3, R^4, and R^5 in each Q is substituted with a bond to L_n,

further provided that when R^2 is 2-aminothiazole-4-acetic acid, K is N-methylarginine, further provided that when R^4 is 2-aminothiazole-4-acetic acid, K

and K' are N-methylarginine, and still further provided that when R^5 is 2-aminothiazole-4-acetic acid, K' is N-methylarginine;

S_f is a surfactant which is a lipid or a compound of the formula:  ;

A^9 is OR^{27};

A^{10} is OR^{27};

R^{27} is $C(=O)C_{1-15}$ alkyl;

E^1 is C_{1-4} alkylene substituted with 1-3 R^{28};

R^{28} is independently selected at each occurrence from the group: R^{30}, $-PO_3H-R^{30}$, =O, $-CO_2R^{29}$, $-C(=O)R^{29}$, $-CH_2OR^{29}$, $-OR^{29}$, and C_1-C_5 alkyl;

R^{29} is independently selected at each occurrence from the group: R^{30}, H, C_1-C_6 alkyl, phenyl, and benzyl;

R^{30} is a bond to L_n;

L_n is a linking group having the formula:

$$(CR^6R^7)_g\text{-}(W)_h\text{-}(CR^{6a}R^{7a})_{g'}\text{-}(Z)_k\text{-}(W)_{h'}\text{-}(CR^8R^9)_{g''}\text{-}(W)_{h''}\text{-}(CR^{8a}R^{9a})_{g'''}$$

W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO_2,

$(OCH_2CH_2)_{20-200}$, $(CH_2CH_2O)_{20-200}$, $(OCH_2CH_2CH_2)_{20-200}$, $(CH_2CH_2CH_2O)_{20-200}$, and $(aa)_t$";

aa is independently at each occurrence an amino acid;

Z is selected from the group: aryl substituted with 0-3 R^{10}, C_{3-10} cycloalkyl substituted with 0-3 R^{10}, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{10};

R^6, R^{6a}, R^7, R^{7a}, R^8, R^{8a}, R^9 and R^{9a} are independently selected at each occurrence from the group: H, =O, C_1-C_5 alkyl substituted with 0-3 R^{10}, and C_1-C_5 alkoxy substituted with 0-3 R^{10}, and a bond to S_f;

R^{10} is independently selected at each occurrence from the group: a bond to S_f, $COOR^{11}$, OH, NHR^{11}, C_{1-5} alkyl substituted with 0-1 R^{12}, and C_{1-5} alkoxy substituted with 0-1 R^{12};

R^{11} is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R^{12}, C_{3-10} cycloalkyl substituted with 0-1 R^{12}, amino acid substituted with 0-1 R^{12}, and a bond to S_f;

R^{12} is a bond to S_f;

k is selected from 0, 1, and 2;
h is selected from 0, 1, and 2;
h' is selected from 0, 1, 2, 3, 4, and 5;
h" is selected from 0, 1, 2, 3, 4, and 5;
g is selected from 0, 1, 2, 3, 4, and 5;

g' is selected from 0, 1, 2, 3, 4, and 5;

g" is selected from 0, 1, 2, 3, 4, and 5;

g"' is selected from 0, 1, 2, 3, 4, and 5;

s is selected from 0, 1, 2, 3, 4, and 5;

s' is selected from 0, 1, 2, 3, 4, and 5;

s" is selected from 0, 1, 2, 3, 4, and 5;

t is selected from 0, 1, 2, 3, 4, and 5;

t' is selected from 0, 1, 2, 3, 4, and 5;

and a pharmaceutically acceptable salt thereof.

42. (original) A method according according to Claim 39, wherein the compound is selected from the group:
1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-(cyclo(Arg-Gly-Asp-D-Phe-Lys)-dodecane-1,12-dione;
1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG3400-α-carbonyl)-cyclo(Arg-Gly-Asp-D-Phe-Lys))-dodecane-1,12-dione; and,
1-(1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamino)-12-((ω-amino-PEG3400-α-carbonyl)-Glu-(cyclo(Arg-Gly-Asp-D-Phe-Lys))$_2$)-Dodecane-1,12-dione.

43. (original) The method according to claim 39, which further comprises a parenterally acceptable and an echogenic gas.

44. (original) The method according to claim 39, further comprising: 1,2-dipalmitoyl-sn-glycero-3-phosphotidic acid, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, and N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine.

45. (original) The method according to claim 43, wherein, the echogenic gas is a C_{2-5} perfluorocarbon.

46. (original) A kit comprising a compound of Claim 39 and a perfusion imaging agent.

47. (original) The method according to claim 1, wherein the vitronectin targeted imaging agent and a perfusion imaging agent have spectrally separable gamma-emission energies.

48. (original) The method according to claim 1, wherein the images are displayed side-by-side to faciliate interpretation of the localization of the vitronectin targeted imaging in the body, relative to the distribution of the perfusion agent in the body.

49. (original) The method according to claim 1, wherein the images are overlayed to faciliate interpretation of the localization of the vitronectin targeted imaging in the body, relative to the distribution of the perfusion agent in the body.

50. (original) The method according to claim 1, for use in concurrent imaging sites of angiogenesis and organ perfusion.

51. (original) The method according to claim 1, for use in diagnosing and localizing sites of angiogenesis and perfusion abnormalities.

52. (original) The method according to claim 1, for use in concurrent detection and localization of sites of endothelial damage and perfusion abnormalities.

53. (original) The method according to claim 1, for use in the concurrent detection and localization of sites of vulnerable plaque and perfusion abnormalities.

54. (original) The method according to claim 1,wherein administering the vitronectin targeted imaging agent and a perfusion imaging agent is concurrent.

55. (original) The method according to claim 1,wherein administering the vitronectin targeted imaging agent and a perfusion imaging agent is sequential.

56. (original) The method according to claim 1,wherein the vitronectin targeted imaging agent and a perfusion imaging agent are administered in a synergystically effective amount.

57. (original) The method according to claim 1,wherein the gamma-emission energies of the vitronectin targeted imaging agent and the perfusion imaging agent are spectrally separable by pulse-height analysis.

58. (original) The method according to claim 1,wherein the difference in gamma emission spectral energies of the vitronectin antagonist diagnostic metallopharmaceutical and the perfusion imaging agent is >10Kev.

59. (original) The method of claim 1 wherein the perfusion imaging agent is a radiolabelled imaging agent, which is radiolabeled with Tc-99m or Tl-201.

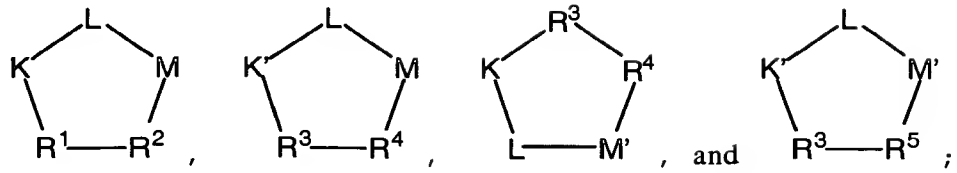
60. (original) The method of claim 4 wherein the ultrasound perfusion agent is comprised of a gaseous microbubble or liquid emulsion.

61. (original) The method of claim 4 wherein the ultrasound perfusion agent is a perfluorocarbon gas.

62. (original) The method of claim 4 wherein the ultrasound perfusion agent is a perfluorocarbon liquid.

63. (original) The method of claim 4 wherein the MRI perfusion imaging agent is comprised of Gd(III), Dy(III), Fe(III), or Mn(II).

64. (original) The method of claim 1, wherein the vitronectin receptor targeted imaging agent comprises a compound Q which is radiolabeled with a radioisotope selected from the group consisting of: ^{123}I, ^{18}F, ^{13}N, and ^{11}C, wherein Q is a peptide independently selected from the group:



, , , and ;

K is an L-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ-N-2-imidazolinylornithine, δ-N-benzylcarbamoylornithine, and β-2-benzimidazolylacetyl-1,2-diaminopropionic acid;

K' is a D-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ-N-2-imidazolinylornithine, δ-N-benzylcarbamoylornithine, and β-2-benzimidazolylacetyl-1,2-diaminopropionic acid;

L is independently selected at each occurrence from the group: glycine, L-alanine, and D-alanine;

M is L-aspartic acid;

M' is D-aspartic acid;

R^1 is an amino acid substituted with 0-1 bonds to the radioisotope, independently selected at each occurrence from the group: glycine, L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, phenylalanine, thienylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, 1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, and methionine;

R^2 is an amino acid, substituted with 0-1 bonds to the radioisotope, independently selected at each occurrence from the group: glycine, valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, methionine, and 2-aminothiazole-4-acetic acid;

R^3 is an amino acid, substituted with 0-1 bonds to the radioisotope, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, and D-methionine;

R^4 is an amino acid, substituted with 0-1 bonds to the radioisotope, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, D-methionine, and 2-aminothiazole-4-acetic acid;

R^5 is an amino acid, substituted with 0-1 bonds to the radioisotope, independently selected at each occurrence from the group: glycine, L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-2-aminohexanoic acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-serine, L-ornithine,

L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, L-cysteine, L-penicillamine, L-methionine, and 2-aminothiazole-4-acetic acid; and

provided that one of R^1, R^2, R^3, R^4, and R^5 in each Q is substituted with a bond to the radioisotope, further provided that when R^2 is 2-aminothiazole-4-acetic acid, K is N-methylarginine, further provided that when R^4 is 2-aminothiazole-4-acetic acid, K and K' are N-methylarginine, and still further provided that when R^5 is 2-aminothiazole-4-acetic acid, K' is N-methylarginine.

65. (original) The method of claim 4 wherein the MRI perfusion imaging agent is selected from the group: trisodium (2(R)-((4, 4-diphenylcyclohexy)(hydroxy)phosphoryloxymethyl) diethylenetriaminopentaacetato(6-))-gadolinate(3-), gadopentetic acid, gadodiamide, and gadoteridol.

66. (original) The method of claim 4 wherein the MRI perfusion imaging agent is the vitronectin receptor targeted imaging agent which is unbound to the vitronectin receptor.

Office Action dated March 11, 2003

In an Office Action dated March 11, 2003, the claims were restricted into the inventions of Groups I to XVIII. Specifically, the Examiner had required restriction under Section 121 between the following Groups:

Group	Claims	Subject Matter[1]	Class
I	1-21, 23-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the sequence, cyclo (Arg-Gly-Asp-Tyr-...Val)	424/1.69
II	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo(Arg-Val-Tyr-Asp-...Gly)	424/1.69
III	1-27, 29-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo (Arg-Gly-Asp-Phe-Lys)	424/1.69
IV	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo(Arg-Gly-Asp-Tyr-Lys)	424/1.69
V	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, Phe-Glu(cyclo(Lys-Arg-Gly-Asp-Phe)-cyclo (Lys-Arg-Gly-Asp-Nal)	424/1.69
VI	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo (Arg-Gly-Asp-Nal-Lys)	424/1.69
VII	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, Glu (cyclo(Lys-Arg-Gly-Asp-Nal)-cyclo(Lys-Arg-Gly-Asp-Nal)	424/1.69

1 The subject matter of the claim refers to a "targeted imaging agent", not a "target" as stated in the restriction into groups of the office action.

Group	Claims	Subject Matter[1]	Class
VIII	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, Glu (O-cyclo (Lys-Arg-Gly-Asp-Phe)-O-cyclo (Lys-Arg-Gly-Asp-Phe)	424/1.69
IX	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, Glu(O-cyclo(Tyr-aminopropyl)-Val-Arg-Gly-Asp)-O-cyclo(Tyr(3-aminopropyl)-Val-Arg-Gly-Asp)	424/1.69
X	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo(Arg-Gly-Asp-Lys(N-5-carbonyl-2-pyridinyl-diazenido)-Val	424/1.69
XI	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo(Lys-5-carbonyl-2-pyridinyl-diazendio-Phe-Asp-Gly-Arg	424/1.69
XII	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, 5-carbonyl-2-pyridinyl-diazenido-Glu-cyclo(Lys-Phe-Asp-Gly-Arg)-cyclo(Lys-Phe-Asp-Gly-Arg)	424/1.69
XIII	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo(Phe-Lys-5-carbonyl-2-pyridinyl-diazenido-Asp-Gly-Arg	424/1.69
XIV	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo(N-Me-Arg-Gly-Asp-ATA-Lys(N-5-carbonyl-2-pyridinyl-diazenido)	424/1.69
XV	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the amino acid sequence, cyclo(Cit-Gly-Asp-Phe-Lys-5-carbonyl-2-pyridinyl-diazenido)	424/1.69
XVI	1-21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent	424/1.69

Group	Claims	Subject Matter[1]	Class
		wherein the targeted imaging agent comprises the amino acid sequence, Glu(cyclo-Lys-Arg-Gly-Asp-Phe)-cyclo(Lys-Arg-Gly-Asp-Phe)	
XVII	1-19, 21-27, 29-41, and 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the compound, Glu-cyclo(Arg-Gly-Asp-Phe-Lys)2-dodecane 1,12-dione	424/1.69
XVIII	1-19, 21, 23-27, 29-41, 43-66	A method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the vitronectin receptor targeted imaging agent is not one encompassed in Groups I-XVII above.	424/1.69

The Examiner had also required an election of species, from among possible vitronectin targeted imaging agents and possible perfusion agents. The Examiner stated that the inventions were unrelated because a search of one vitronectin receptor targeting agent as set forth in the groups above would neither anticipate nor render obvious the sequences in the other groups, even though the use is the same. The Examiner further stated that each peptide sequence represents a patentably distinct product with distinct physical and chemical properties.

The Office Action required an election of species for search purposes. Claims 1-66 allegedly disclose a plurality of patentably distinct species comprising vitronectin receptor targeted imaging agents and perfusion imaging agents. Applicant was requested to elect a single disclosed species for a vitronectin receptor imaging agent and a perfusion imaging agent.

Response dated May 12, 2003

Applicant filed a Response to the Restriction Requirement on May 12, 2003. Applicant elected *with traverse* to prosecute the claims of Group XVI. Further, Applicant elected, *with traverse*, a species where the perfusion imaging agent is Tl-201, as described on page 53, ¶ 59, and the vitronectin receptor targeted imaging agent is the ^{99m}Tc-tricine-TPPTS complex of [[5-[carbonyl]-2-pyridinyl]diazenido]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}, as described in Example 39, page 200. Applicant

also requested that should the Examiner consider the elected species allowable, consideration of the full generic scope of pending Claims 1 to 22, 23 to 27, 29 to 41 and 43 to 66 be considered.

Applicant further requested that in the event that the Examiner should decide to maintain a restriction under 35 U.S.C. § 121, rather than treat the election as a provisional election of species, Applicant proposed an alternative restriction to four groups of claims and parenthetically stated the relationship to the Examiner's groups. The proposed four groupings of claims were based on the amino acid sequence of the binding domain found on vitronectin for the vitronectin receptor, *e.g.*, Arg-Gly-Asp, and variations thereof.

Office Action dated September 10, 2003

In an Office Action dated September 10, 2003, the Examiner made the restriction requirement final, but modified the restriction as suggested in Applicant's response filed May 12, 2003. The subject matter of modified Group I was examined. Modified Group I encompassed claims 1-66 drawn to a method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeting agent has one of a group of defined amino acid sequences. The Examiner further stated that the claims were not searched beyond modified Group I, and requested that all subject matter not directed to the elected group be deleted.

In other matters addressed in the Office Action, claims 39 and 56 were rejected under 35 U. S. C. § 112, second paragraph, as allegedly being indefinite, Claims 1-7, 9, 38, 39, 47-63, 65, and 66 were provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claims 1-5, 29, 30, and 39-59 of copending Application No. 10/213,713. Claims 8, 10-37, 40-46, and 64 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. No prior art rejections were made. These matters are addressed in an Amendment and Response, submitted concurrently with this Petition.

POINTS TO BE REVIEWED

Applicant's claims are directed to imaging methods that comprise, in part: (a) administering a vitronectin receptor targeted imaging agent and a perfusion imaging agent; and (b) concurrently detecting the vitronectin receptor targeted imaging agent bound at the vitronectin receptor and the perfusion imaging agent. Dependent claims further define the nature of the vitronectin receptor targeted imaging agent, and/or the nature of the perfusion imaging agent. For example, dependent Claim 6 specifies that the vitronectin receptor targeted imaging agent is a diagnostic metallopharmaceutical. Claim 9, which depends from Claim 6, further defines the metallopharmaceutical, specifying that it comprises a metal and a compound, wherein the compound comprises, *inter alia*, a targeting moiety and a chelator capable of chelating the metal. Claim 16, which depends from Claim 9, further specifies that the metal is a radioisotope selected from a recited group of radioisotopes. Claim 19, which depends from Claim 16, specifies that the radioisotope is ^{99m}Tc. Finally, Claim 20, which depends from Claim 19, states that the vitronectin receptor targeted imaging agent may be selected from a group of 19 species of ^{99m}Tc radiopharmaceuticals. Similarly dependent Claims 22, 28, and 42 identify vitronectin receptor targeted imaging agents that may be selected from a group of particular species of radiopharmaceuticals.

In the Office Action dated March 11, 2003, it was asserted that each of the individual species of radiopharmaceuticals set forth in dependent Claims 19, 22, 28, and 42 (except where the species share the same targeting moiety) represents a separate invention, and the Examiner issued a restriction requirement under 35 U.S.C. § 121 on this basis. Applicant traversed the restriction requirement on the basis that the Office Action improperly treated what should have been a request for an election of species into an 18-way restriction under 35 U.S.C. § 121.

As an initial matter, according to MPEP § 803, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 802.01, § 806.04, § 808.01) or distinct as claimed (see MPEP § 806.05-§ 806.05(i)); ***and***

(B) There must be a serious burden on the examiner if restriction is not required (see MPEP § 803.02, § 806.04(a) - § 806.04(i), § 808.01(a), and § 808.02).

In a Response dated May 12, 2003, Applicant argued that the Examiner had not established a *prima facie* case of a serious burden. For purposes of the initial requirement, a serious burden may be *prima facie* shown if the examiner shows separate classification, separate status in the art, or a different field of search as defined in MPEP § 808.02. In the subject application, the Examiner had restricted the claims into 18 different groups. However, ***all 18 groups are classified in Class 424/1.69.*** Applicant argued that the Examiner had not established a *prima facie* case of a serious burden.

Moreover, the restriction requirement imposed in the Office Action improperly identifies particular ***species*** that are recited in Markush-type claims, which in turn are further connected by generic linking claims, as separate inventions. Applicant respectfully submits that any restriction among the members of the Markush groups within the claims should only be made provisionally. MPEP § 803.02 which addresses restriction practice with respect to Markush-type claims, clearly sets forth that the Examiner may only require a ***provisional*** election of a single species prior to examination on the merits. The provisional election would be given effect in the event that the Markush-type claim was found not to be allowable. Following election, the Markush-type claim should be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim were not allowable over the prior art, examination would be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration. However, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim would then be extended to the full scope of the generic claims.

The MPEP provides an example in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D, and E. With such a claim, the examiner may require a ***provisional*** election of a single species, CA, CB, CC, CD, or CE. The Markush-type claim is then examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If, on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species would be rejected, and claims to the non-elected species would be held withdrawn from

further consideration. On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim would then be extended.

As discussed above, the method comprising administering a vitronectin receptor targeted imaging agent in Claim 1, is referred to in several layers of dependent claims, before finally reaching dependent Claim 20, which sets forth specific examples of ^{99m}Tc radiopharmaceuticals. More than one species of an invention, not to exceed a reasonable number, may be specifically claimed in different claims within one application. *See* 37 C.F.R. § 1.141. Applicant respectfully submits that the specific compounds set forth in dependent Claim 20 are a reasonable number of species of the generic claim 1.

The generic method defined by Claim 1 is a single claimed invention under 35 U.S.C. § 121. The further elements added in dependent Claims 2 to 66 further define the invention set forth in Claim 1. It is respectfully submitted that these dependent claims, and the groups of compounds set forth therein, do not define independent inventions. The specific radiopharmaceutical compounds set forth in Claim 20 act by the same mode of operation and are each capable of use for the same function. The peptides function as targeting moieties for integrins by binding to integrin receptors, for example, the vitronectin receptor. Each of the radiopharmaceutical compounds has the same classification, as acknowledged by the Examiner, in Class 424/1.69. Each of the radiopharmaceutical compounds of Groups I to XVIII provides the same function and acts by the same general mechanism in methods defined by the more generic claims. The mechanism by which these common peptide sequences act as vitronectin receptor targeting agents, finds support in the specification, for example, page 83, l. 25 to p. 84, l. 21.

In Applicant's previous response, it was proposed that if the Examiner intended to maintain a restriction under 35 U.S.C. § 121, rather than treat Applicant's election as a provisional election of species, Applicant proposed an alternative restriction to the following four groups of claims and parenthetically stated the relationship to the Examiner's groups:

I. Claims 1-66, drawn to a method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the sequence, Arg-Gly-Asp.
(This encompasses the Examiner's groups I, III, IV, V, VI, VII, VIII, IX, X, XIV, XVI, XVII.)

II. Claims 1-21, 23-27, 29-41, 43-66, drawn to a method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the sequence, Asp-Gly-Arg.
(This encompasses the Examiner's groups XI, XII, XIII.)

III. Claims 1-21, 23-27, 29-41, 43-66, drawn to a method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the sequence, cyclo Arg-D-Val-D-Tyr ... D-Asp-Gly.
(This encompasses the Examiner's group II.)

IV. Claims 1-21, 23-41, 43-66, drawn to a method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the sequence.
(This encompasses the Examiner's group XV.)

The proposed four groupings of claims are based on the amino acid sequence of the binding domain found on vitronectin for the vitronectin receptor, *e.g.*, Arg-Gly-Asp, and variations thereof, Asp-Gly-Arg, cyclo Arg-D-Val-D-Tyr ... D-Asp-Gly, and cyclo Cit-Gly-Asp-D-Phe-Lys -5-carbonyl-2-pyridinyl-diazenido.

In an Office Action dated September 10, 2003, the Examiner modified the restriction to modified Groups I through IV, which differs from Applicant's proposed Groups I through IV. The restriction requirement was deemed proper and was therefore made final. The Examiner chose to examine a modified Group I which differs from Applicant's proposed Group I.

The Examiner's modified Group I comprises a Markush group wherein the targeting agent has specified amino acid sequences. The Examiner's modified Group I is to Claims 1-66, drawn to a method of imaging comprising administering a vitronectin receptor targeted

imaging agent wherein the targeting agent has the sequences, cyclo (Arg-Gly-Asp-Tyr-...Val) (see claim 20, first compound on page 245); cyclo (Arg-Gly-Asp-Phe-Lys) (see claim 20, second compound on page 246); cyclo(Arg-Gly-Asp-Tyr-Lys) (see claim 20, third compound on page 246); Phe-Glu(cyclo(Lys-Arg-Gly-Asp-Phe)-cyclo (Lys-Arg-Gly-Asp-Nal) (see claim 20, fourth compound on page 246); cyclo (Arg-Gly-Asp-Nal-Lys) (see claim 20, fifth compound on page 246); Glu (cyclo(Lys-Arg-Gly-Asp-Nal)-cyclo(Lys-Arg-Gly-Asp-Nal) (see claim 20, sixth compound on page 246); Glu (O-cyclo (Lys-Arg-Gly-Asp-Phe)-O-cyclo (Lys-Arg-Gly-Asp-Phe) (see claim 20, eighth compound on page 246); Glu(O-cyclo(Tyr-aminopropyl)-Val-Arg-Gly-Asp)-O-cyclo(Tyr(3-aminopropyl)-Val-Arg-Gly-Asp) (see claim 20, compound bridging pages 246-247); cyclo(Arg-Gly-Asp-Lys(N-5-carbonyl-2-pyridinyl-diazenido)-Val (see claim 20, first complete compound listed on page 247, lines 4-5); cyclo(N-Me-Arg-Gly-Asp-ATA-Lys(N-5-carbonyl-2-pyridinyl-diazenido) (see claim 20, compound listed in lines 17-18 on page 247); Glu(cyclo-Lys-Arg-Gly-Asp-Phe)-cyclo(Lys-Arg-Gly-Asp-Phe) (see claim 22, first compound on page 248); and Glu-cyclo(Arg-Gly-Asp-Phe-Lys)2-dodecane1,12-dione (see claim 42, last compound on page 262).

Additionally, the Examiner asserted that the claims were not searched beyond the scope of modified Group I, and requested that all non-elected subject matter be deleted. It would appear, therefore, that the Examiner is requiring that Claim 1 be amended to include a Markush group that is limited to the specific targeting sequences of modified Group I. Applicant respectfully submits that this requirement improperly denies Applicant the full scope of his invention.

ACTION REQUESTED

Applicant respectfully requests reconsideration of the restriction requirement, and in particular to consider it only a provisional election of species for the purpose of carrying out the search. Applicant has already elected, *with traverse*, the compounds of modified Group I (Claims 1-66, drawn, in part, to a method of imaging comprising administering a vitronectin receptor targeted imaging agent wherein the targeted imaging agent comprises the sequence as described above). The Examiner has apparently conducted a search of these compounds, and has not identified any relevant prior art that would defeat the patentability of such